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Sex differences in clinical characteristics of dry eye disease

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Title

Sex differences in clinical characteristics of dry eye disease.

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Abstract

Purpose: To investigate the role of sex on the symptomatology of DED and on the associations between symptoms and signs.

Methods: A cross-sectional study was used including 755 dry eye patients from the Groningen Longitudinal Sicca Study (GLOSSY cohort). Patient symptoms were assessed by the Ocular Surface Disease Index (OSDI) questionnaire and dry eye signs by the six most commonly used tests. Patients were divided in groups based on overall severity of signs and within these groups total and specific symptoms were compared by sex. Sex differences in Spearman correlation between symptoms and signs were calculated.

Results: Women had higher total symptom scores than men in both the mild (33.8 vs 24.7, P=0.01) and moderate signs groups (38.3 vs 28.0, P<0.005), but this difference was less apparent in the severe signs group (40.4 vs 37.2, P=0.33). Independent of severity of signs, women consistently reported more light sensitivity than men (P<0.01 in all groups). The correlation between symptoms and overall severity of signs score was significantly lower in women (ρ =0.11 vs ρ =0.33 in men, P=0.01), with clearest differences between women and men in correlations with Schirmer (ρ= 0.01 vs ρ =-0.21, P=0.03) and TFBUT (ρ =-0.08 vs ρ =-0.30, P=0.02).

Conclusions: This large clinical study has shown that sex has a large influence on the symptomatology of DED, with significantly higher symptom scores and lower correlation between symptoms and signs in women compared to men. These findings are of importance in clinical practice and in conducting research into DED.

Key words: dry eye disease; epidemiology; gender; neuropathic dry eye; sex; signs; symptoms.

1. Introduction

The importance of sex and gender disparities and the need to account for sex as a biological variable is being increasingly emphasized in medical research.[1] In Ophthalmology there are notable sex differences in many traits and diseases, but very little is known about root causes to enable design and implementation of diagnostic, preventive and treatment strategies.[2] Dry eye disease (DED) is no exception, as numerous epidemiological studies have shown that DED is far more prevalent in women than in men and biological studies have shown that sex has a major influence on the regulation of the ocular surface and adnexa.[3, 4] Different underlying mechanisms of pathophysiology have been proposed, such as a possible important role for sex steroids and other hormone imbalances in women.[4] However, despite all the epidemiological and biological studies, there is still a surprisingly lack of knowledge about the influence of sex in clinical characteristics of DED. To our knowledge, only one study has reported sex differences in total symptoms of DED, showing more symptoms in women.[5] However, there have been no reported studies investigating sex differences in clinical characteristics of DED, including both symptoms and signs and their correlation. Indeed, the recently published TFOS DEWS II report on *Sex, gender and hormones*[4] advocated the need for further studies to clarify the precise nature and extent of sex and gender effects on DED, with a special need for epidemiological studies using data on both signs and symptoms, and for studies investigating differences in diagnostic tests between men and women. Therefore, this study aimed to explore the role of sex in the clinical characteristics of dry eye patients, using a large tertiary dry eye patient cohort. We investigated sex differences in both the symptomatology of DED and the association between DED symptoms and the most commonly tested signs in clinic.

2.Methods

2.1 Study sample

The GLOSSY (Groningen LOngitudinal Sicca StudY) cohort is a clinic-based cohort of dry eye patients from the tertiary dry eye clinic at the University Medical Center Groningen in the Netherlands. General and ophthalmic medical history, dry eye symptoms, dry eye test results using standardized methods, and dry eye therapies have been recorded longitudinally since September 2014, resulting in a clinical cohort with data on approximately 1500 patient visits a year. The University Medical Center Groningen is a national referral center for Sjögren syndrome, and consequently, almost half of the patients visiting the tertiary dry eye clinic are Sjögren patients. All patients recruited to the GLOSSY cohort until December 2016 were included in this study. These patients have either dry eye diagnosed by an ophthalmologist and/or are under the care of the multidisciplinary Sjögren syndrome service. No further exclusion criteria were applied. The study was approved by the Institutional Review Board (IRB) of the University Medical Center Groningen. The research followed the tenets of the Declaration of Helsinki. Information on sex was derived from the patient's passport, which represents biological sex. To our knowledge, there were no transsexuals in our cohort.

2.2 Assessment of dry eye symptoms

All patients completed the Ocular Surface Disease Index (OSDI) at the beginning of their visit. The OSDI, developed by the Outcomes Research Group at Allergan Inc (Irvine, California), is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning.[6] Presence of symptoms during the last week is rated per item on a five-

point scale (0-4) from 'none of the time' to 'all of the time'. The OSDI total score (ranging from 0-100) can be calculated with a formula that uses the sum score of all completed questions. In a similar way, scores from the 3 OSDI subscales (i) ocular symptoms, (ii) vision-related functions, and (iii) environmental triggers can be calculated by looking at questions 1-5, 6-9 and 10-12, respectively.[6]

2.3 Assessment of dry eye signs

Dry eye tests were performed in both eyes, in the following order: tear osmolarity, Schirmer test without anaesthesia, staining of the cornea with fluorescein, tear fluorescein breakup time (TFBUT), staining of the nasal and temporal conjunctiva with lissamine green, and Meibomian gland dysfunction. Ophthalmologists that graded the dry eye were not aware of the study question. Tear osmolarity was measured from the inferior lateral meniscus with a laboratory-on-a-chip by the *TearLab Osmolarity System (San Diego, Ca*) following standard protocols.[7] An unanaesthetized Schirmer-1 value after 5 minutes (mm/5 min) using sterile strips was measured following standard protocols.[7] Staining of the cornea with fluorescein was performed using the Oxford Schema grading, ranging from grade 0 to 5, based on the number of punctate dots for the total exposed inter-palpebral cornea.[7] Staining of the conjunctiva with lissamine green was performed in a similar way using the Oxford Schema grading, scoring both the temporal and nasal zone and taking the sum of these scores per eye, ranging from 0 to 10.[7] TFBUT was measured by instilling a drop of fluorescein counting the seconds after a blink before the tear film was broken up, following standard protocols.[7] The median score of three measurements per eye was taken. Meibomian gland dysfunction was scored by taking the average of the quality score (0 clear; 1 cloudy; 2 granular; 3 toothpaste) and the expressibility score (0 minimal; 1 light; 2 moderate; 3 heavy pressure needed) of the meibum.[8] Each of the 6 dry eye tests was transformed to a common unit severity score

between 0 and 1, with 0 being no sign of DED at all and 1 being the highest severity grade of DED for that test. Subsequently, an overall severity of signs score was calculated for each patient by taking the mean severity score of these 6 tests. For more information on how this score was exactly calculated see Vehof et al.[9]

2.4 Statistical analysis

First, descriptive statistics were used to describe the characteristics of the study population, stratified by sex. Patients were divided into three groups based on the patient's overall severity of signs score: mild (0-0.24), moderate (0.25-0.49) and severe signs (0.5-1.0), to reflect the dry eye severity grading scheme proposed by DEWS as closely as possible.[10] Then, within groups total OSDI symptom scores and specific symptom scores were compared between men and women, using Mann-Whitney U-tests. Subsequently, Spearman correlations between total OSDI symptom score and signs were calculated, stratified by sex. Differences in correlations between sex were tested for statistical significance by using Fisher's r-to-z transformation for correlation coefficients in independent samples, testing the null hypothesis that ρ_1-ρ_2=0.[11] Data were analyzed with the SPSS statistical package (version 23.0; SPSS, Inc). A P-value lower than 0.05 was considered statistically significant in all analyses.

3. Results

The first consecutive 755 DED patients from the GLOSSY cohort were included. The majority was female (n=607, 80.4%) and the mean age was 56.1 (standard deviation 15.7) years. Table 1 shows the demographics and the prevalence of self-reported comorbidities, stratified by sex. The prevalence of chronic pain syndromes, Sjögren syndrome, osteoarthritis, the presence of any allergy, and thyroid disease were all higher in women, consistent with distribution of these diseases in the general population. Men had a significantly higher use of

beta-blockers and higher prevalence of graft-versus-host disease. Table 2 shows the mean signs and symptoms stratified by sex. Women, on average, had higher total symptoms score, but also higher tear osmolarity, higher corneal and conjunctival staining scores, and lower TFBUT. Schirmer scores and Meibomian gland dysfunction did not significantly differ between groups. Women were consequently more frequently categorized in the groups with higher overall severity of signs scores. However, within each of these three groups the severity of signs scores were not significantly different between men and women, indicating an equal level of signs in men and women within the mild, moderate and severe signs groups.

Figure 1 shows the total OSDI symptoms scores, stratified by overall severity of signs and sex. In the mild and moderate signs groups, women had significantly higher total symptom scores than men (being around 40% higher score in women in both groups). This difference was however not as apparent in the severe signs group, where men and women had more similar total symptom scores (around 8% higher in women, P=0.33). Looking at the specific symptoms from the OSDI (Figure 2), within the mild and moderate signs groups women had higher scores than men on particularly light sensitivity and an uncomfortable feeling in windy conditions, low humidity and air conditioned areas. In the severe signs group there were no clear sex differences in specific symptoms, with the exception of only light sensitivity, again reported significantly more by women than by men, suggesting it is a female-specific symptom independent of severity of signs.

In Figure 3 the correlations between DED signs and total symptoms score are presented for the total sample. The correlation coefficient of symptoms with overall signs severity score was only 0.11 (P=0.009) in women and a higher 0.33 (P<0.0005) in men (P-value for a difference = 0.01) indicating that, in general, women show significantly lower correlation

between symptoms and signs. Largest sex differences in correlations between symptoms and specific signs were found with Schirmer value (women ρ =0.01 (P=0.84) versus men ρ =-0.21 (P=0.02), P-value for a difference =0.03), and TFBUT (women ρ =-0.08 (P=0.06) versus men ρ =-0.30 (P=0.001), P-value for a difference =0.02). Sex differences in correlation between symptoms and overall sign severity score were visible in all signs severity groups, but most pronounced in the severe signs group: mild signs women ρ=0.15 (P=0.13), men ρ=0.28 (P=0.06); moderate signs women ρ=0.07 (P=0.28), men ρ=0.22 (P=0.10); severe signs women ρ=0.02 (P=0.82), men ρ=0.47 (P=0.001).

4. Discussion

To our knowledge, this study is the first *clinical* study specifically looking at sex differences in clinical characteristics of DED patients. Our results showed that, even when corrected for severity of signs, female dry eye patients tend to be more symptomatic than men, especially when only mild or moderate signs are present. An uncomfortable feeling with environmental triggers like wind and air-conditioning, and particularly light sensitivity are symptoms that were identified as female specific symptoms. Perhaps most intriguing, women showed significantly lower correlations between symptoms and signs. These results are important to realize in clinical practice and critical in designing or analyzing studies, where subgroup analyses or stratification seems to be inevitable

The finding of increased dry eye symptoms even with similar severity of clinical signs and the lack of association of symptoms with signs in women compared to men could be the result of several underlying mechanisms. First, there might be sex differences in the sensitivity of the ocular surface. Several studies, in differing settings, showed at least some evidence of

increased corneal or conjunctival sensitivity in women, although this sex difference might depend on factors such as pre- or postmenopausal status, and might vary between mechanical, chemical and thermal sensitivity.[12-16] Other studies however did not find any sex difference in corneal sensitivity.[17, 18] Future studies are needed to confirm and further explore these differences, but also to clarify the exact role of ocular surface sensitivity in the symptomatology of DED.

Second, sex differences in general pain sensitivity might play a role. There is extensive literature on this topic, and it has been shown that the female sex is an important risk factor for many clinical pain conditions, including chronic pain syndromes, widespread pain, and neuropathic pain.[19] A literature review of sex differences in experimental pain perception concluded that women had a consistently lower pain tolerance for cold pain, hot pain and pressure pain.[20] Our group has shown in a large sample of female volunteers that dry eye symptoms were associated with both higher pain sensitivity and lower pain tolerance, as tested by a heat stimulus on the forearm, indicating the link between dry eye symptoms and general pain sensitivity.[21] In an extended sample of this twin cohort we have shown that the chronic pain syndromes irritable bowel syndrome, fibromyalgia and pelvic pain show shared genetic factors with DED, indicating that DED is, at least partly, part of a spectrum of chronic pain disorders.[22] So, given all these findings together, it might not be surprising that the present study found women to have lower correlation between symptoms and signs. That dry eye involves more than the ocular surface alone is increasingly recognized. In the recently published *TFOS DEWS II Definition and Classification Report*[23] neuropathic dry eye was added in the classification scheme of dry eye, in addition to the well-recognized evaporative and aqueous deficient dry eye. In the present study women particularly reported increased light sensitivity and an uncomfortable feeling due to environmental triggers such as air

conditioning and wind. Interestingly, exactly these symptoms have been linked to ocular neuropathic pain in other studies.[24, 25] So, the more frequent report of these specific symptoms and the lower correlation between symptoms and signs in women, might all point to an increased frequency of neuropathic dry eye in women as compared to men.

Third, the role of gender might also be an important factor explaining our results. Where sex refers to the anatomy of an individual's reproductive system and functions that derive from the chromosomal complement, gender refers to a person's self-representation as male or female or how that person is responded to by social institutions on the basis of the individual's gender presentation.[26] As the feminine gender role is generally associated with a greater willingness to report pain[4], this might be another cause of increased OSDI scores in our female patients.

Fourth, women are more at risk for the majority of comorbidities that are risk factors of DED[3, 4, 27], such as allergies, chronic pain syndromes, depression, anxiety, and autoimmune diseases such as Sjögren syndrome. This is also reflected in our sample (see Table 1). Difference in distribution of underlying etiologies could also lead to altered symptomatology between men and women. For example, non ocular studies have shown that depression and pain are highly comorbid and that depression can lead to increased pain.[19] Moreover, in persons with a depression, women are more likely to report pain complaints than men.[28] On top of that, in a study looking at the discordance between symptoms and signs in DED we have shown that the presence of chronic pain syndromes, allergies and depression are all associated with relatively more symptoms than signs.[9] However, the presence of Sjögren syndrome was associated with the opposite.

In addition, the more diffuse group of etiologies in female dry eye patients might also mathematically have a major influence on the correlation between symptoms and signs. A hypothetical illustration of this is given in Table 3: combining two subgroups of dry eye patients, each with a perfect correlation between symptoms and signs, can result in a very low correlation of almost zero if the subgroups differ greatly in mean symptoms and/or sign scores. This difference in mean signs and/or symptoms between subgroups could easily be the case in dry eye, where for example patients with chronic pain syndromes have higher symptom scores without accompanying worse clinical signs[29] and Sjögren patients have similar symptoms despite higher sign scores compared to other patients[30]. The example in Table 3 also may, in part, supply an explanation for the well-known lack of correlation between signs and symptoms in DED: unless a 'pure' group of DED patients including only one underlying etiology is studied, correlations may be low. So, given the multifactorial pathophysiology of DED and our current findings, stratification on subgroups based on sex and/or underlying aetiology in studies might be more important than we realize.

To our knowledge, ours is the first study to take into account the severity of signs, but we are not the first to report greater symptoms in women; Schaumberg et al investigated sex differences in symptoms in 581 men and 1518 women with self-reported diagnosis of dry eye, using a questionnaire that included the OSDI.[5] They found significantly higher symptoms in female than in male dry eye patients (total OSDI score of 29.0 vs 18.5, $P<0.0001$), which was present across all 3 subscales of the OSDI, similarly with the highest difference in the environmental triggers subscale. Compared to their patient cohort, our patients had a total OSDI score that is around 10 points higher in both men and women, which reflects the severity of patients in our tertiary dry eye clinic compared to a questionnaire based self-report of a dry eye diagnosis. Schaumberg et al did however not test for dry eye signs, and results

must be interpreted with caution as men and women were selected from different populations, with differences in education level and age of inclusion, which could have confounded results.

Our findings reflect our cohort from a tertiary dry eye clinic with a relatively large group of Sjögren patients. This might limit the generalizability to other DED patient cohorts. However, as a crude sensitivity analysis, we found similar sex differences in correlation between overall signs severity score and symptoms in non-Sjögren patients (women ρ=0.12, men ρ =0.30) as in primary (women ρ =0.18, men ρ =0.31) and secondary (women ρ =0.13, men ρ =0.28) Sjögren dry eye patients. Although we included the most commonly tested signs in our study, another limitation might be that symptoms in female dry eye patients are better captured by other tests. We recommend further research in this area. A strength of this study is the large sample size of the GLOSSY cohort and the systematic assessment of the dry eye tests, using standardized protocols, that were all performed in one center. Our study has the required large sample size with sufficient power to detect a difference in correlation coefficients between men and women.

In conclusion, this study found that sex has an important effect on the clinical characteristics of DED. This finding has important consequences for the interpretation of outcomes in both clinical practice and clinical studies, and further studies are needed to find out how to best address this in the diagnostics and treatment of DED. DED studies, like most studies in medicine, rarely stratify on sex, and our findings clearly underline the importance of this.

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Figure 1: Sex differences in total dry eye symptoms, stratified by overall severity of signs (total n=755).

Error bars represent 95% confidence intervals.

Figure 2: Sex differences in specific dry eye symptoms, stratified by overall severity of signs: **a)** mild dry eye signs, **b)** moderate dry eye signs, and **c)** severe dry eye signs.

Error bars represent 95% confidence intervals.

Figure 3: Sex differences in the correlation between dry eye signs and symptoms.

MGD = Meibomian Gland Dysfunction. TFBUT = Tear Fluorescein Breakup Time.

Table 1: Demographics and comorbidities of dry eye disease patients, stratified by sex.

	Men (n=148)	**Women (n=607)**	**P-value for a difference**
Age (yrs) (mean, sd)	55.0 (15.5)	56.4 (15.8)	0.47
Self reported comorbidity / use of medication (%):			
Depression	7	7	0.73
Chronic pain syndrome	6	21	<0.0005
Chronic fatigue syndrome	2	4	0.37
Diabetes	6	5	0.46
Osteoarthritis	5	20	<0.0005
Rheumatoid Arthritis	16	20	0.1
GVHD	10	2	<0.0005
Thyroid disease	7	16	0.001
Sjögren syndrome	22	51	<0.0005
Allergy (any)	7	18	0.008
Asthma	10	12	0.41
Hayfever	8	14	0.3
Eczema	11	13	0.36
Contact lens user	3	3	1.00
Postmenopausal	n/a	65	n/a
Use of betablockers	25	16	0.009
Use of antidepressants	7	8	0.36
Use of antihistamines	3	9	0.04
Use of diuretics	11	12	0.79

N/a: not applicable. Sd: standard deviation. GVHD: Graft-versus-host disease.

Table 2: Mean symptoms and signs of dry eye disease patients, stratified by sex.

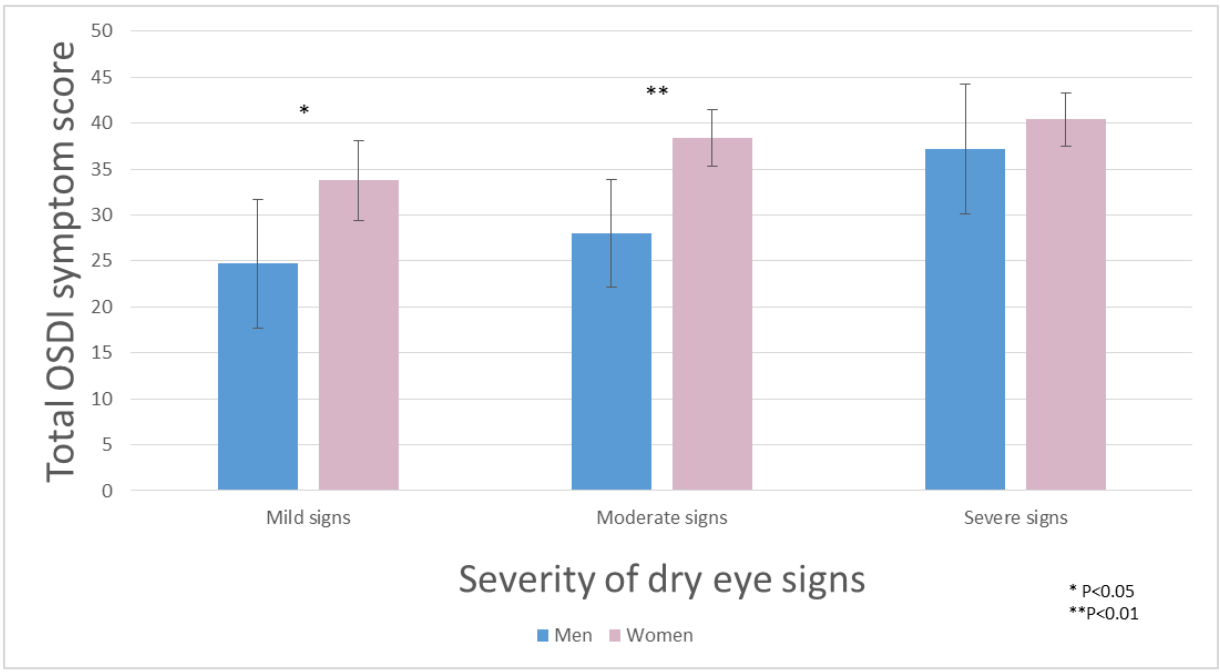
	Men (n=148)	Women (n=607)	P-value for a difference
Total OSDI symptom score	29.9 (23.9)	38.3 (24.3)	<0.0005
Ocular symptoms subscale	29.8 (24.4)	37.2 (24.1)	<0.0005
Vision related function subscale	27.0 (28.7)	31.7 (28.3)	0.22
Environmental triggers subscale	38.6 (33.1)	51.4 (33.5)	<0.0005
Overall signs severity score	0.34 (0.20)	0.39 (0.19)	0.004
Corneal staining (Oxford, 0-5)	1.41 (1.43)	1.62 (1.36)	0.048
Conjunctival staining (Oxford, 0-10)	2.15 (2.38)	2.79 (2.75)	0.027
Schirmer (mm/5 mins)	6.80 (13.3)	6.60 (16.8)	0.31
TFBUT (s)	5.4 (3.7)	4.4 (3.2)	0.01
Tear osmolarity (mOsm/l)	309.5 (17.5)	316.0 (19.4)	0.004
MGD score (0-3)	0.98 (0.90)	0.90 (0.87)	0.31
Signs severity group			0.01
Mild	44 (29.8%)	110 (18.1%)	
Overall signs severity score within mild signs group	0.12 (0.05)	0.13 (0.06)	0.28
Moderate	57 (38.5%)	249 (41.0%)	
Overall signs severity score within moderate signs group	0.33 (0.09)	0.32 (0.08)	0.18
Severe	47 (31.8%)	248 (40.9%)	
Overall signs severity score within severe signs group	0.56 (0.12)	0.57 (0.12)	0.56

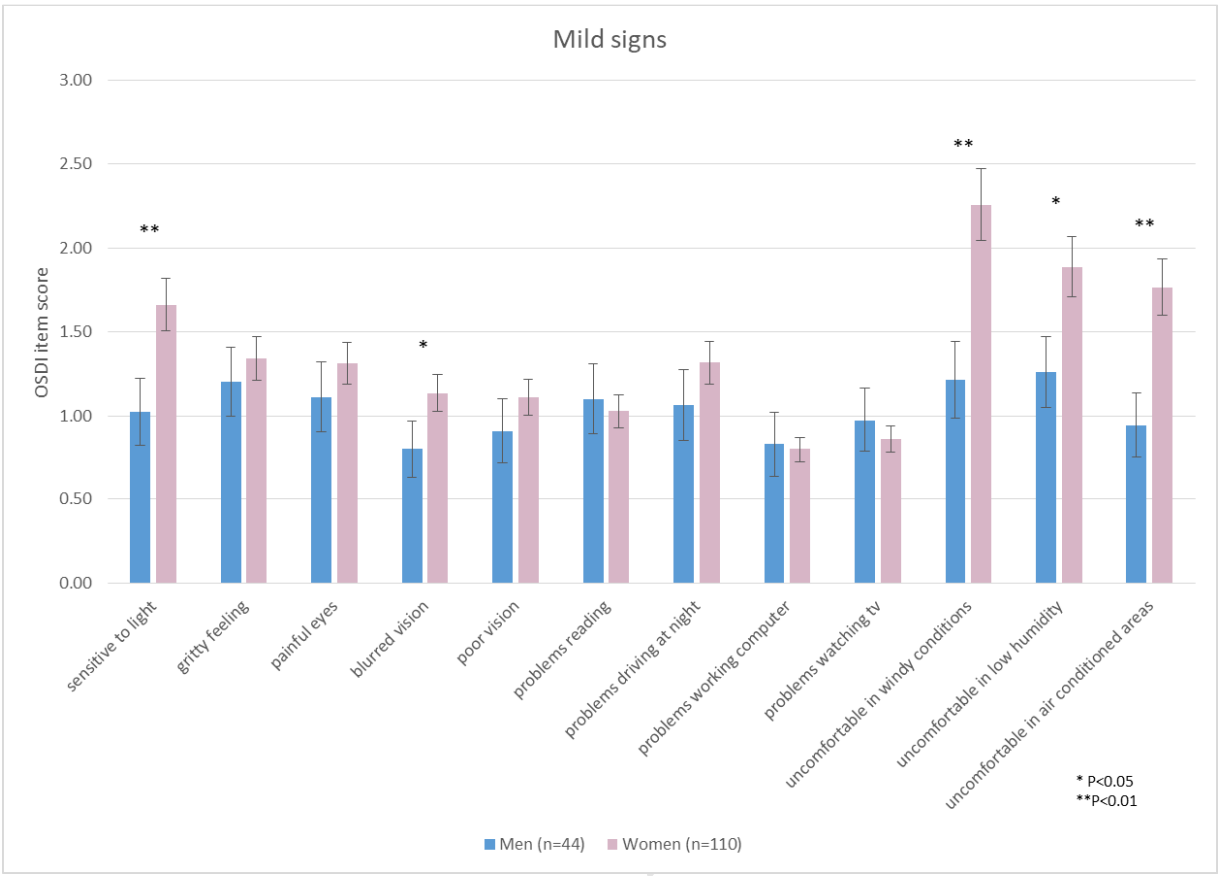
Mean (standard deviation) or n (%) are given. OSDI = Ocular Surface Disease Index. TFBUT= Tear fluorescein breakup time. MGD = Meibomian gland dysfunction.

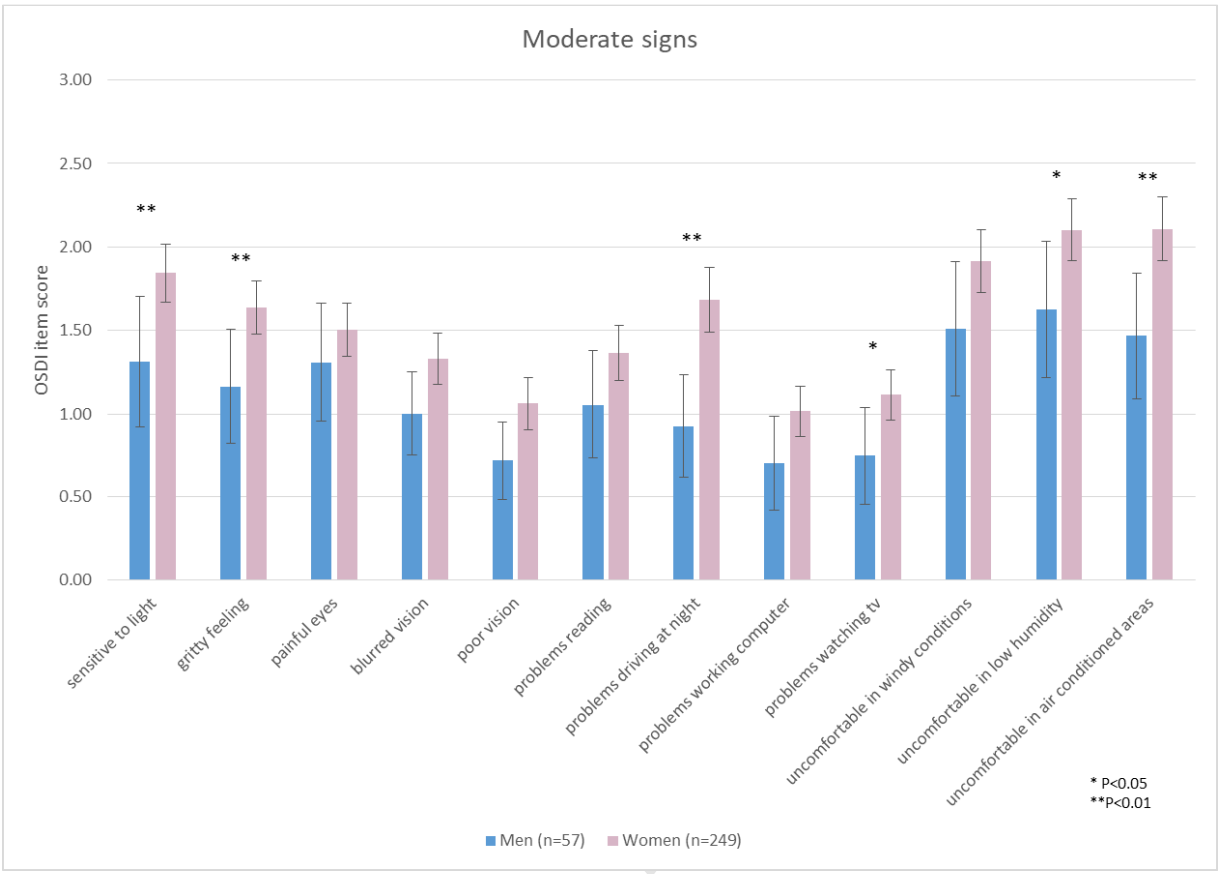
Table 3: Hypothetical illustration of how combining subgroups of dry eye patients could lead to a dramatic fall in correlation coefficient between symptoms and signs.

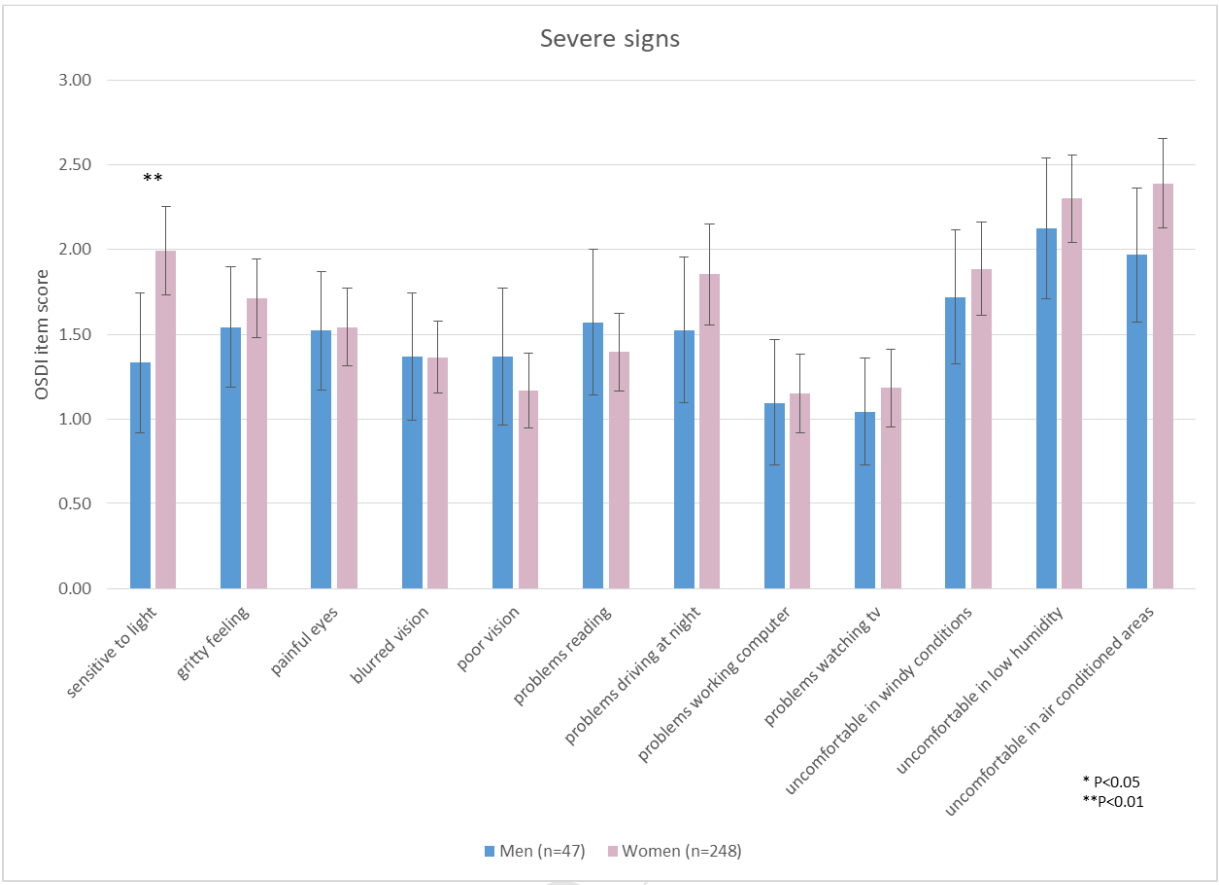
Dry eye patients with Sjögren syndrome (n=10)		*Dry eye patients with chronic pain syndrome (n=10)*		*Combined Sjögren syndrome and chronic pain syndrome dry eye patients (n=20)*	
Sign score	Symptom score	Sign score	Symptom score	Sign score	Symptom score
2	1	1	7	2	1
4	2	2	9	4	2
6	3	3	11	6	3
8	4	4	13	8	4
10	5	5	15	10	5
12	6	6	17	12	6
14	7	7	19	14	7
16	8	8	21	16	8
18	9	9	23	18	9
20	10	10	25	20	10
Correlation: 1.00		Correlation: 1.00		1	7
				2	9
				3	11
				4	13
				5	15
				6	17
				7	19
				8	21
				9	23
				10	25
				Correlation: 0.06	

In this illustration, dry eye patients with Sjögren syndrome and chronic pain syndromes both show a perfect correlation of 1.00 between symptom and sign scores. Because Sjögren patients tend to have relatively more signs than symptoms, and chronic pain syndrome patients tend to have relatively more symptoms than signs, the correlation between symptoms and signs drops dramatically to 0.06 if the two groups are combined.








Severe signs
OSDI item score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
**
sensitive to light
gritty feeling
painful eyes
blurred vision
poor vision
problems reading
problems driving at night
problems working computer
problems watching tv
uncomfortable in windy conditions
uncomfortable in low humidity
uncomfortable in air conditioned areas
* P<0.05
**P<0.01
Men (n=47)
Women (n=248)